

ON THE RELATION OF EPITHELIOMA TO IRRITATION AND CHRONIC INFLAMMATION.*

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THE connection between irritation and cancer has attracted the attention of so many clinical observers, and has been the subject of so many hypotheses by pathologists, that even a short recapitulation of the views of the most distinguished would considerably break into the time at my disposal. I will, therefore, at once describe some anatomical facts, which, I trust, may in some measure elucidate this difficult question.

The following is a case of epithelioma of a tongue, which had been affected with chronic superficial glossitis for years.

Henry W., aged 48, was admitted to St. Bartholomew's Hospital with the following history. Six months ago, he noticed a pimple on the side of the tongue, which was followed by an ulcer. The tongue had been very peculiar for years past; it had been very smooth, and covered with white patches (chronic superficial glossitis). He had been a great smoker until the last four or five months, smoking generally a short clay-pipe. Had constitutional syphilis twenty-eight years ago, but the tongue was not affected.

A large warty ulcerated mass of epithelioma occupied a considerable portion of the right half of the dorsum and side of the tongue; the left half was smooth, devoid of papillæ, and here and there covered with small white thin patches like scar-tissue.

Microscopic Appearances.—Sections taken from the margin of the epithelioma to the tip of the tongue, including about one inch of apparently unaffected epithelium, showed that the surface was devoid of papillæ, and covered by a thin layer of cornified epithelium, which, at a point near the epithelioma, presented a well-marked fissure (See Fig. 1). From the deep stratum of the epithelium, numerous branched and club-shaped processes, apparently corresponding to the normal convexities of the epithelium in the interpapillary furrows, extended down into the submucous tissue, which was throughout the section thickened and infiltrated with "indifferent cells". The ingrowths from the epithelium were larger, more highly branched, and extended further downwards as the epithelioma was approached; but the gradation was not regular, and the commencement of any considerable enlargement of the interpapillary processes was abrupt. (See Fig. 1.) Epithelial "cell-nests" made their appearance in the extremities of the processes, and in the superficial layer of epithelium, at that portion of the section which adjoined the epithelioma. The fully developed growth presented the characters of the tubular epithelioma of Cornil and Ranvier.

Mr. Butlin, in a paper on Smooth Tongue—chronic superficial glossitis—(*Med.-Chir. Trans.*, vol. lxi, p. 51), gives the result of the examination of "three of these tongues, which were removed because the disease, in each case, was complicated by epithelioma, occurring

* Read before the Pathological Section of the British Medical Association at Cambridge.

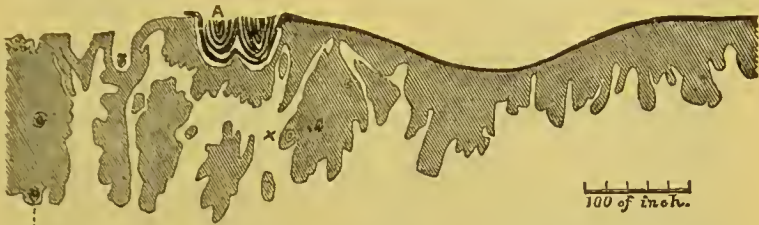
after it had existed for some years". He observes that, in some parts, the epithelium "dipped down at irregular intervals into the subjacent tissues, so that a rough kind of papillary appearance was produced. These downward processes were much more common and much larger as the epithelioma was approached." This condition is well shown in Fig. 11 of his paper. In the same paper, Mr. Butlin expresses the opinion that, "in everything except the thickening of the epidermis, the microscopic anatomy is precisely the same in psoriasis (ichthyosis) and chronic superficial glossitis". (*Op. cit.*, p. 55.)



Fig. 1.—Portion of a Section of the Epithelium of a Tongue affected with chronic superficial glossitis, in the neighbourhood of an epithelioma, showing commencing ingrowth from the deep stratum of the epithelium. (A.) Portion of the section adjoining the epithelioma. 4 in. obj.

A case of ichthyosis was recently admitted into the hospital, which was in an unusually favourable condition for the study of the connection between this disease and epithelioma. One half of the tongue was removed, because it was thought that the disease had, or would soon, become epitheliomatous; yet the characteristic appearances of epithelioma were absent. The patient was a solicitor, aged 64. The epithelium of the tongue was generally thickened and whitish over the left half of the dorsum, from the tip to a point somewhat behind the middle of the tongue; and there were two rather abruptly raised patches of thickened epithelium—one at the margin, the other on the adjoining portion of the dorsum. The surface of these raised patches was white, hard, irregular, and pitted, from the presence of small corn-like masses of epithelium. In the centre of the thickened patch at the margin, there was a slightly depressed but not ulcerated surface. The patient had suffered from a sore tongue for ten years. The primary cause he believed to be the irritation of the tongue by some jagged and carious teeth, which he was ultimately obliged to have removed, on account of the rubbing of the sore tongue against them. This explanation is the more probable, as the more highly affected portions of the tongue corresponded in position to the affected teeth. He first noticed permanent patches on the tongue three years and a half before his admission. During the last three months, the tongue had become much more painful. Microscopic examination of the raised patches described showed a thick layer of cornified epithelium on the surface, which in many places was depressed or dipped down, so as to form plugs of cornified epithelium, having somewhat the appearance and structure of a corn, and composed of curved strata or laminae

of flattened epithelial cells (see Fig. 11). From the deep stratum of the epithelium, numerous round and club-shaped processes extended down into the submucous tissue, often as far as the muscular tissue (see Fig. 11).



Cell-Nests.

Fig. 11.—Outline of the Epithelium of the Tongue from a case of ichthyosis, showing a gradually increasing ingrowth of epithelium. The larger ingrowths contain “cell-nests”.—A. Corn-like masses of cornified epithelium.

In sections taken from the thickened patch at the margin of the tongue (Fig. 11), many of these processes contained cell-nests (see Fig. 111); but only one or two were found in sections taken from the patch on the dorsum. Sections, taken from portions of the tongue slightly affected with ichthyosis, showed smaller interpapillary prolongations downwards of the epithelium, with occasional small depressions of the thick layer of cornified epithelium on the surface, and corresponding larger ingrowths from the deep stratum, containing rarely indications of a cell-nest. (See Fig. 1v.) The submucous tissue was everywhere thickened and infiltrated with “indifferent cells”, which were more thickly aggregated where the downward prolongations of the epithelium were largest.



Fig. 111.—Cell-Nests indicated by a x in Fig. 11.

No better or more well-known example of cancer following irritation can be found than in epithelioma of the scrotum of chimney-sweeps; and the anatomical evidence of their direct relation as cause and effect is, I think, as clear as the clinical. I have examined three specimens of chimney-sweeps' cancer with special reference to this point.

Sections in one case, taken from portions of the scrotum at a distance

from the epithelioma, appearing normal or perhaps with some slight

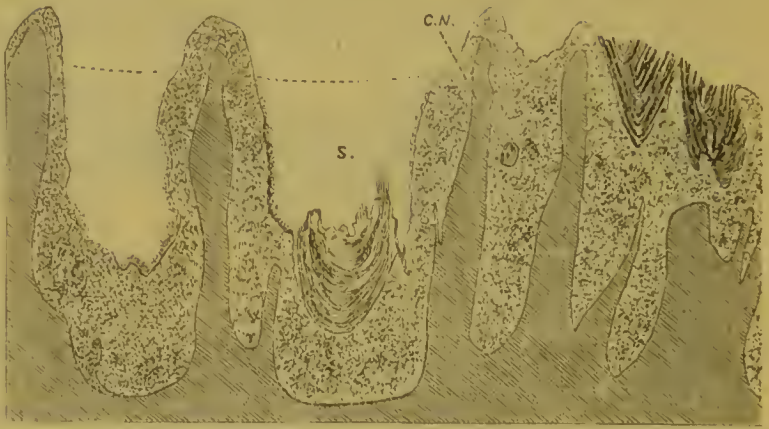


Fig. iv.—More slightly affected portion of Ichthyotic Tongue. s. Space left from the breaking away of a mass of laminated cornified epithelium. C.N. Cell-Nest. The dotted portion of the diagram represents the epithelium, the interpapillary processes of which are prolonged downwards.

thickening and roughening of the skin, showed a very considerable elongation of the interpapillary processes of the rete Malpighii, around which numerous “indifferent cells” were scattered (see Fig. v).

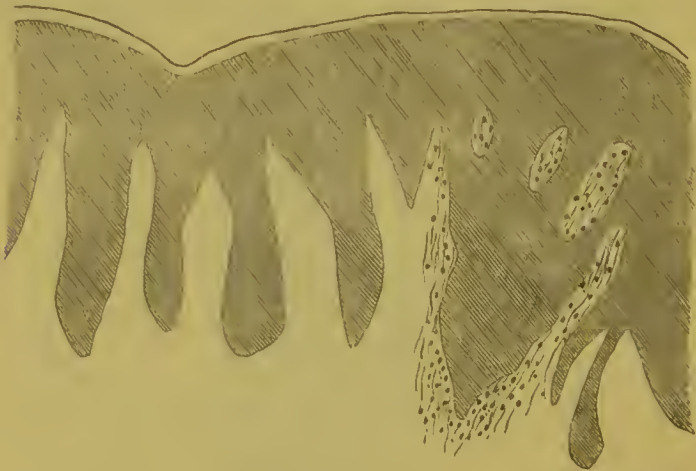


Fig. v.—Outline of the Epithelium of a Scrotum irritated by soot, showing slight ingrowth of the interpapillary processes of the rete.

Similar and more marked appearances were observed in a portion of the skin of the perinæum, removed in another case of epithelioma of the scrotum on account of two warts, one of which had existed for four years. Sections of one of these warts, and of a small warty growth in another case, showed, in addition to an overgrowth of epithelium on the surface and thickening of the corium, a distinct ingrowth of epithelium in the form of papilla-like processes. Sections of portions of epithelioma

in an early stage of formation presented ingrowths of epithelium, constituting merely an exaggeration of the elongation of the interpapillary processes seen in the warts and irritated skin (see Fig. vi). It could also be plainly observed that the sebaceous glands participated in the epithelial ingrowths.



Fig. vi. Outline of the Epithelium from a portion of an Epithelioma of the Scrotum, in an early stage of formation.

The repeated recurrence of epithelioma of the scrotum after removal is another indication of the general nature of the change in the skin, quite coinciding with the anatomical appearances described above.

The following case is an instance of a functional hypertrophy of the skin giving place to epithelioma.

George H., aged 56, was admitted into Darker Ward with an epithelioma* on the under surface of the heel, about the size of a crown-piece. The surface was hard, warty, and fissured, but not ulcerated; the edges were raised by a heaping up of epithelium.

The patient stated that, eight years ago, he noticed a hard corn on the under surface of the heel, which he used to have cut every week. After having existed a considerable time, the corn became warty and began to increase in size. Two years ago, the growth was removed, but, recurring, it was again excised with a similar result. Finally, the foot was amputated by Mr. Willett.

Microscopic Appearances.—The surface of the growth was covered by a moderately thick layer of cornified epithelium, from which large columns, composed of concentric laminæ of cornified epithelium, extended deeply into the tumour. At the margin of the epithelioma, there was a great heaping-up of uncornified cuticle, and, from the deep stratum of the rete Malpighii, numerous long pointed anastomosing papilla-like processes extended down into the corium; this change was observed for a considerable distance beyond the margin of the morbid growth.

* Specimen in the Museum of St. Bartholomew's Hospital, No. 3325.

Briefly reviewing and connecting the anatomical appearances observed in these cases, we find in a tongue affected with ichthyosis—a chronic inflammatory process—changes in the superficial epithelium with an elongation of the interpapillary processes of the deep stratum; while, in more highly affected portions of the tongue, a gradual transition, from this slight ingrowth of epithelium to fully developed epithelioma, could be observed. In the tongue affected with chronic superficial glossitis, the ingrowth from the epithelium extended so far beyond the margin of the epithelioma, that it cannot be accounted for by the gradual extension of the disease, but is more reasonably referred to the antecedent inflammatory process; an opinion supported by other similar cases.

Finally, in portions of the skin of the scrotum and perinæum, long irritated by the friction of soot between their folds and against garments, we have a similar ingrowth from the deep stratum of the rete, associated with evidences of irritation, such as infiltration of the corium with leucocytes, etc.; and also the formation of warts, showing the same tendency to ingrowth from the deep stratum of the epithelium.

In view of the facts, one cannot do otherwise than refer the general slight ingrowth of the epithelium, both in the scrotum and tongue, to the long continued irritative or inflammatory process existing in each case; and, since no definite line can be drawn between this slight ingrowth of epithelium and the widely extending ingrowth constituting epithelioma—a direct transition from the one into the other being observable—there is the strongest evidence that the inflammatory or irritative process is the direct cause of the cancer, by occasioning the first disturbance of the boundary-line between the epithelium and connective tissue. Recent observations* on those cases of cancer of the breast following eczema of the nipple tend to show that there is a chronic inflammatory condition of the nipple, which, extending into the lacteal ducts, induces a growth of columns of epithelium from the sides of the ducts (duct-cancer of Waldeyer), which may be considered analogous to the columns extending down from the epithelium in epithelioma.

In prepuces affected with balanitis associated with specific or non-specific sores, I found on the mucous surface, in places, a distinct elongation and occasional branching of the interpapillary processes of the rete; but where the inflammation was more acute, as at the margin of the sores, the leucocytes extended into the overgrown epithelium and destroyed it. This would appear to furnish the explanation why the acuter forms of inflammation of the skin and mucous membrane are never followed by epithelioma; while long continued chronic inflammatory processes, observed in ulcers of the integuments, and old patches of skin-disease, occasionally are.

Some light may be thrown on the mode of production of epithelioma, by briefly glancing at the relation between an outgrowth of epithelium (as in callosities, corns, and warts, etc.), and the ingrowth of epithelium constituting epithelioma. That there is a close connection between the two processes is shown by the cases already referred to—viz., of ichthyosis, of warts† on the scrotums of chimney-sweeps, and of a corn giving rise to epithelioma. As further examples, I will allude to the following cases. There is a specimen (No. 1789), of epithelial cancer of the tongue in the museum of St. Bartholomew's Hospital, in which "the disease commenced eight years

* See papers by Mr. H. T. Butlin, *Transactions Medico-Chirurgical Society*, vol. lx, p. 153; and Dr. Thin, *Proc. Med.-Chir. Soc.*, p. 442, 1880.

† With regard to irritation as a cause of warts, see *Wagner's Pathology*, p. 393.

before death in a small, hard, white lump on the middle of the dorsum of the tongue, at a spot on which the end of a tobacco-pipe had often rested. The patient was for several years in the habit of paring this lump with a razor." Recently a mason, aged 48 years, was admitted to the hospital with an epithelioma on the palm of the hand, which grew in the situation of a callosity. In the above-mentioned museum, there are some horny growths (No. 2822) of considerable length, removed from the scrotum of a chimney-sweep, where they had existed some months. During nine years five similar growths had formed, and had been shed. This specimen shows that an irritation, which usually gives rise to epithelioma, may sometimes cause merely an outgrowth of epithelium. There is also another specimen of a portion of scrotum (No. 2821), with a large horny growth, side by side with a warty infiltrating growth, which I find on examination to be an epithelioma.

Quite recently I examined a flat, sessile, finely nodulated warty growth about the size of a half-crown, removed by Mr. T. Smith from the perinæum of a gentleman, aged 35 years. It had been growing there years, and the patient, who had resided in hot climates, attributed its growth to the irritation of garments and the sweating about the parts, which occasioned sometimes intense itching. It was growing rapidly when removed, but presented all the appearances of a simple flat wart. The microscopic characters showed, even more distinctly than the warts on the scrotum described above, the transition from simple hypertrophy of epithelium to epithelioma. There was decided, but not extreme, thickening of the cuticle, which dipped down in places; and from the rete Malpighii, long anastomosing papillæ, containing many "cell-nests", extended down into the thickened corium; but the general arrangement of the different portions of the cutis was not entirely lost.

If time permitted, I could cite other cases bearing on the same point; but these appear to me sufficient to indicate that the borderline between the so-called hypertrophies of epithelium and epithelioma is of the slightest description, and that a continuance of the causes which give rise to the former, may lead to the latter.

There is some evidence to show that the overgrowth of superficial epithelium constituting a callosity or corn—a functional hypertrophy of the part—is due to a reactive hyperæmia, produced by the irritation, just as an irritation of the conjunctiva is followed by injection. If a corn be injected, a distinct red line is seen at its base, due to the dilated and numerous vessels of the corium beneath: the growth of epithelium in this case appears somewhat analogous to that which took place in the cock's spur in Hunter's remarkable experiment (see Sir J. Paget's *Lectures on Pathology*, p. 53); the spur, when transplanted to the comb, where the blood-supply was augmented, grew in a spiral form to a length of six inches.

A striking instance of overgrowth of the Malpighian layer of the skin from increased blood-supply fell under my observation in a case of aneurysm by anastomosis,* involving the whole pinna of the ear, and originating in a small nævus. Sections taken from several portions of the skin of the ear showed that the interpapillary processes of the epithelium of the ear were very considerably elongated, in some places extending down into the corium as branched processes (see Fig. vii), resembling those seen in the early stage of epithelioma. This observation is extremely suggestive in regard to the production of epithelioma,

* See *Transactions of the Pathological Society*, vol. xxi, p. 88, 1880.

especially when considered in connection with the known tendency of nævi, vascular moles, etc., to become the seats of malignant growths.



Fig. VII.—Outline of the Epithelium of the Pinna of the Ear from a case of aneurysm by anastomosis, showing ingrowth of the interpapillary processes of the rete Malpighii.

For if an inflammatory hyperplasia may be the starting-point of the epithelial ingrowth, why may not an overgrowth of epithelium from simple increased blood-supply prove an equally efficient cause?

It is not the object of this paper to maintain that epitheliomata are necessarily produced by some form of irritation, but to show, that the anatomical evidence of the direct relation between irritative and inflammatory processes and epithelioma is entirely in accordance with clinical observation, that a long-continued chronic inflammation or an irritation of moderate intensity are direct causes of epithelioma, doubtless frequently favoured by certain conditions, such as hereditary and constitutional tendency, and the nutritive conditions accompanying advanced age (see Thiersch, *Der Epithelialkrebs*, p. 80).

It is conceivable that the hyperæmia and nutritive disturbance, thus produced, renew a latent activity and induce a new formation of epithelium after the same manner as the ingrowth from the epiblast, by which the glands and hair-follicles of the skin are formed in the embryo.

Relation to Treatment.—The fact that, in some cases of chronic inflammation and in widely extended irritation—as in chimney-sweeps' cancer—there is an ingrowth from the epithelium for some distance beyond the epithelioma, is, I think, of importance in relation to treatment. For, if the larger of these ingrowths around the epithelioma be not removed, it is probable that, unless destroyed by suppuration, they will grow more rapidly as the result of the hyperæmia around the wound, and produce a speedy recurrence of the disease. I would, therefore, suggest that in these cases especially a very free removal is indicated.

The tendency which warty and other papillary growths exhibit to become the starting point of epithelioma, is a strong indication for their early removal, especially when their origin can be referred to some form of irritation.

[N.B.—All the above diagrammatic sketches are drawn to scale.]